Systematic Review and Meta-Analysis

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Selection of patients with ovarian cancer who may show survival benefit from hyperthermic intraperitoneal chemotherapy

A systematic review and meta-analysis

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Abstract

Background: The use of hyperthermic intraperitoneal chemotherapy (HIPEC) after cytoreductive surgery has been extensively studied in patients with peritoneal carcinomatosis from various malignancies. However, the effectiveness of HIPEC for ovarian cancer is still controversial. Therefore, we performed this meta-analysis to identify patients with ovarian cancer who can obtain survival benefit from HIPEC.

Methods: Articles regarding HIPEC in the MEDLINE, EMBASE, and Cochrane Library were searched till December 2018. In total, 13 case-control studies and two randomized controlled trials were included in this meta-analysis. We investigated the effect of HIPEC on disease-free survival (DFS) and overall survival (OS), and performed subgroup analyses based on the study design, adjustment of confounding variables, and quality of the study.

Results: HIPEC improved both DFS (hazard ratio [HR], 0.603; 95% confidence interval [CI], 0.513–0.709) and OS (HR, 0.640; 95% CI, 0.519–0.789). In cases of primary disease, HIPEC improved DFS (HR, 0.580; 95% CI, 0.476–0.706) and OS (HR, 0.611; 95% CI, 0.376–0.992). Subgroup analyses revealed that HIPEC did not improve OS but improved DFS of patients with residual tumors $\leq$1 cm or no visible tumors. In cases of recurrent disease, HIPEC was associated with better OS (HR, 0.566; 95% CI, 0.379–0.844) but not with DFS. Subgroup analyses also revealed similar tendencies. However, HIPEC improved DFS of patients with residual tumors $\leq$1 cm or no visible tumors, while it improved OS of only those with residual tumors $\leq$1 cm.

Conclusions: HIPEC may improve DFS of patients with ovarian cancer when residual tumors were $\leq$1 cm or not visible. It may also improve OS of only patients with recurrent disease whose residual tumors were $\leq$1 cm.

Abbreviations: CI = confidence interval, DFS = disease-free survival, FIGO = Federation of Gynecology and Obstetrics, HIPEC = hyperthermic intraperitoneal chemotherapy, HR = hazard ratio, IDS = interval debulking surgery, NAC = neoadjuvant chemotherapy, NOS = Newcastle-Ottawa Scale, OS = overall survival, RCT = randomized controlled trial.

Keywords: hyperthermic intraperitoneal chemotherapy, meta-analysis, ovarian cancer

Editor: Jianxun Ding.

SIK and JC contributed equally as first authors.

This work was supported by grants from the Seoul National University Hospital (No. 2320150140), the Korean Health Technology R&D Project, Ministry of Health of Welfare (HI17C0929), and Samyang Corp. (No. 1707–040–867; No.800–20180373).

The authors have no conflicts of interest to declare.

Supplemental Digital Content is available for this article.

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How to cite this article: Kim SI, Cho J, Lee EJ, Park S, Park SJ, Seol A, Lee N, Yim GW, Lee M, Lim W, Song G, Chang SJ, Kim JW, Kim HS. Selection of patients with ovarian cancer who may show survival benefit from hyperthermic intraperitoneal chemotherapy: a systematic review and meta-analysis. Medicine 2019;98:50 (e18355).

Received: 19 June 2019 / Received in final form: 26 September 2019 / Accepted: 13 November 2019

http://dx.doi.org/10.1097/MD.0000000000018355

1. Introduction

Peritoneal carcinomatosis develops in more than 80% of patients with advanced ovarian cancer, resulting in a 5-year survival rate of <50%.[1,2] In terms of the biologic aspect of intraperitoneal dissemination of tumors, peritoneal carcinomatosis is considered the terminal status of cancers, resulting in poor prognosis. However, there is no effective method for treating peritoneal carcinomatosis from most solid tumors, and both surgical resection and systemic chemotherapy have shown minimal effects on survival.[3,4]

In particular, hyperthermic intraperitoneal chemotherapy (HIPEC) after cytoreductive surgery has been extensively studied in patients with peritoneal carcinomatosis from various malignancies, with an improvement in the survival rate and reduction in the recurrence rate.[5,6] Compared to conventional intraperitoneal chemotherapy, HIPEC has several advantages, even showing synergistic effects. Hyperthermia itself has direct cytotoxicity on tumors and increases the penetration of chemotherapy and drug concentration at the peritoneal surface. Moreover, HIPEC can decrease catheter-related complications observed after conventional intraperitoneal chemotherapy because it is conducted in a single session.[7]

Till date, only 2 randomized controlled trials (RCTs) have evaluated the effect and safety of HIPEC for ovarian cancer.[8,9] Spiliotis et al reported that HIPEC resulted in survival benefit for patients with recurrent ovarian cancer.[8] However, that study had limitations considering the randomization process and the definition of the end-points, both of which affect the interpretation of the results.[10] In the other RCT performed by van Driel et al, better disease-free survival (DFS) and overall survival (OS) were observed in patients treated with neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) and HIPEC, compared to those treated with NAC followed by IDS alone.[9] However, the small sample size resulted in an intergroup difference of only 15 deaths, and the different effects of HIPEC among centers make it hard to justify the practical application of HIPEC in the clinical setting.[11] Moreover, a previous meta-analysis did not provide the exact pooled hazard ratios (HRs) associated with HIPEC for evaluating the effect.[12]

Thus, precise knowledge regarding the exact impact of HIPEC on the prognosis of ovarian cancer is still needed, owing to the heterogeneity in the study population, such as primary or recurrent disease, and the extent of cytoreductive surgery among the previous studies. In particular, the identification of patients with ovarian cancer who can benefit from HIPEC will allow for the implementation of individualized treatment. For this purpose, we performed a meta-analysis to investigate the effect of HIPEC on the survival of patients with ovarian cancer.

2. Methods

2.1. Search strategy and selection criteria

This meta-analysis was conducted in accordance with the recommendations per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[13] Studies investigating the effect of HIPEC on the prognosis of ovarian cancer were identified via a literature search of the MEDLINE, EMBASE, and Cochrane Library, from when recording began up to December 2018. Our overall search strategy included the following terms for HIPEC ("hyperthermic intraperitoneal chemotherapy" or "HIPEC" or "intraperitoneal"), ovary ("ovarian" or "ovary"), and cancer ("cancer" or "carcinoma" or "neoplasm" or "malignancy", or "tumor"). Details about the search strategy are shown in Supplementary Table 1, http://links.lww.com/MD/D497.

We included relevant studies that met the following criteria: studies that included patients with epithelial ovarian cancer; study designs included RCT, case-control, and 2-arm cohort studies; and comparison of DFS or OS between patients who underwent HIPEC and those who did not receive it. However, we excluded the following studies: review articles, case reports, editorials, and letters to the editor; studies that had no data of survival or did not meet the selection criteria; and non-English literature.

As the present meta-analysis was performed based on previously published studies, thus no ethical approval and patient consent are required.

2.2. Selection of studies

Two authors (SIK and SJP) independently screened the eligibility of all studies retrieved from the database according to the predetermined selection criteria. The third author (HSK) resolved any disagreement between the 2 authors after discussion. A total of 11,728 studies were identified, and we excluded 3615 duplicates. We excluded 7972 studies because of the following reasons: non-English literature (n=381), non-original articles (n=1275), studies on other cancers (n=1613), translational studies (n=1477), animal studies (n=1082), studies on other treatment modalities (n=1866), and studies dealing with other issues (n=278). In addition, we excluded 126 non-relevant articles after assessing the full-text articles. Finally, 13 case-control studies[14–26] and 2 RCTs[8,9] with 1314 patients were included in the meta-analysis (Fig. 1).

2.3. Data extraction

Two authors (SIK and EJL) independently extracted the data, and any discrepancies were addressed by a joint re-evaluation of the article with the third author (HSK). The following data were extracted from each study for the meta-analysis: author; year of publication; country in which the study was performed; study design; disease status (primary disease, platinum-sensitive and platinum-resistant recurrence); the International Federation of Gynecology and Obstetrics (FIGO) stage; histology; grade; age; numbers of patients who received HIPEC and who did not receive it; drugs and methods of HIPEC; the extent of cytoreductive surgery (or residual tumor size after cytoreductive surgery); follow-up period; DFS and OS; and HRs with 95% confidence intervals (CIs).

For the study with only the HR and *P* value of the Cox proportional hazards model,[14] we estimated the 95% CI mathematically. If patients treated with HIPEC were regarded as the reference group, the HRs were inverted and 95% CIs were subsequently calculated.[16,22,26] In case of studies in which the risk parameters were not presented with specific numbers, we could obtain the estimated risks with 95% CIs by analyzing survival curves[8,15,18–20,24–26] according to the statistical procedure described by Tierney et al.[27]

2.4. Quality assessment

The methodological quality of the 13 case-control studies were evaluated based on the Newcastle-Ottawa Scale (NOS).[28] The NOS includes eight items over three dimensions: selection,

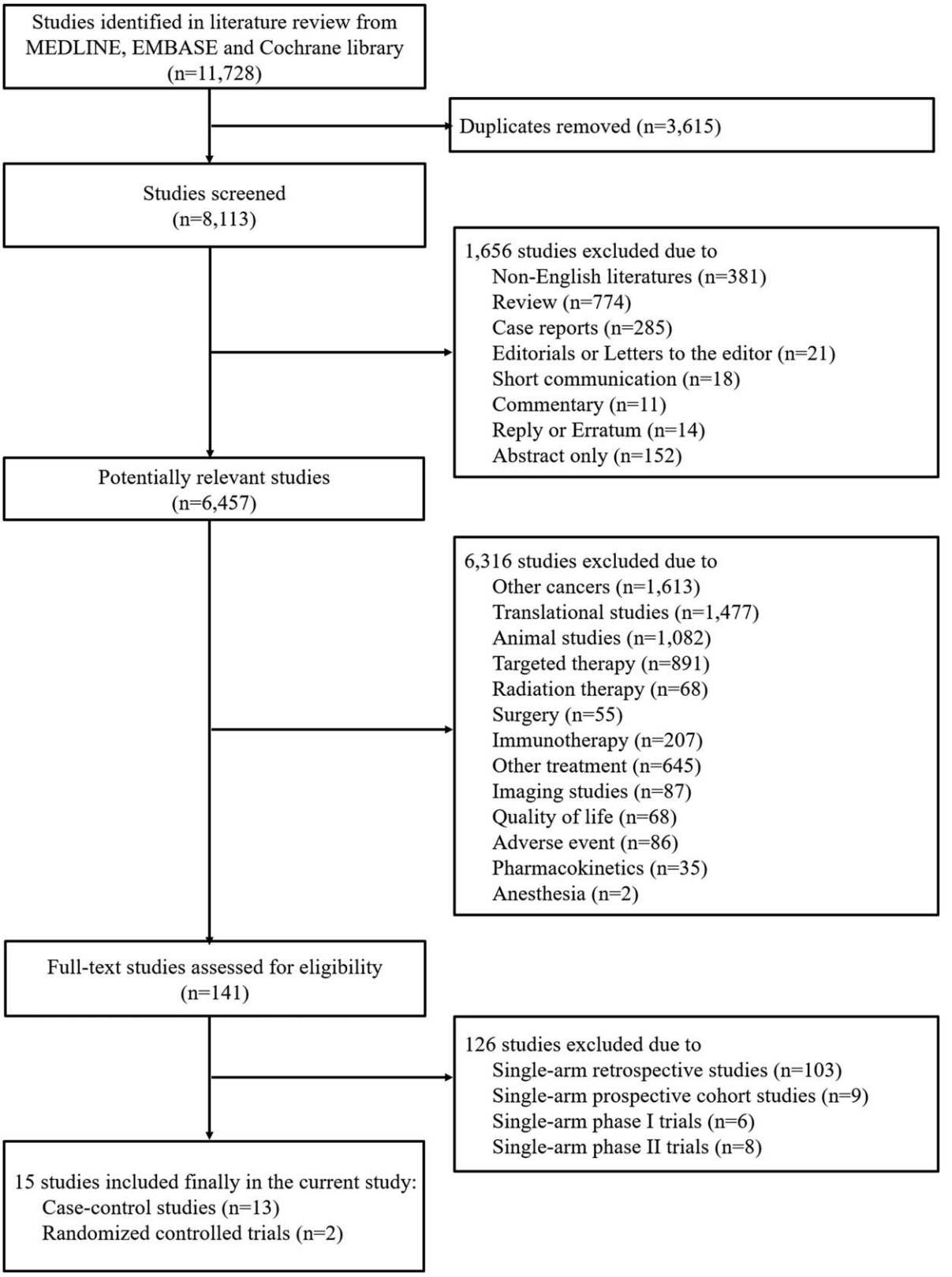

Figure 1. The search strategy and number of studies identified for inclusion in this meta-analysis.

comparability, and exposure with a maximum of 4, 2, and 3 points, respectively. In this meta-analysis, 11 of 13 case-control studies scored 8 showing "high quality", whereas the other 2 studies scored 6 showing "low quality" (Supplementary Table 2, http://links.lww.com/MD/D498).

2.5. Statistical analysis

Pooled HRs with 95% CIs were calculated in all studies, and heterogeneity was assessed by using the Higgins I^2 value that represented the percentage of the total variance in the summary estimate owing to inter-study heterogeneity rather than chance.[29] A value of $>50\%$ was considered to have substantial heterogeneity, and we used the random effects model with the DerSimonian and Laird method. When the I^2 value was $\leq 50\%$, we used the fixed effect model with the Mantel–Haenszel method. In the fixed effect model, each study was weighted by the inverse of its variance.

Subgroup meta-analyses were performed based on the study design, adjustment of confounding variables, and quality of the study. To identify the publication bias, funnel plots were used, where each study's HR and standard error of the log HR were plotted on the X-axis and Y-axis, respectively. We observed symmetric funnel plots, implying no publication bias in this meta-analysis. The Egger test results also showed the absence of publication bias (Supplementary Figure 1, http://links.lww.com/MD/D499).

All statistical analyses were performed with Comprehensive Meta-analysis Version 2.0 (Biostat Inc., Englewood, NJ), and a $P < .05$ was considered statistically significant. All statistical tests were two-sided.

3. Results

3.1. Effect of HIPEC on survival by study design

The characteristics of the 13 case-control studies and two RCTs including 1,314 patients are shown in Table 1. Potential confounding variables such as age, FIGO stage, histology, grade, and residual tumor size at the first surgery were adjusted in most of the studies. In all the studies, HIPEC improved both DFS (HR, 0.603; 95% CI, 0.513–0.709) and OS (HR, 0.640; 95% CI, 0.519–0.789; Fig. 2A). On subgroup analyses confined to the case-control studies, HIPEC improved DFS (HR, 0.575; 95% CI, 0.471–0.702)[14,17,18,20,22–26] and OS (HR, 0.613; 95% CI, 0.398–0.944; Fig. 2B).[14–19,21,22,24–26]

3.2. Effect of HIPEC on survival by disease status

For cases of primary disease, five studies including 630 patients showed that HIPEC was associated with better DFS (HR, 0.580; 95% CI, 0.476–0.706),[9,14,17,20,26] and 5 studies including 591 patients also showed that HIPECT was associated with improved OS (HR, 0.611; 95% CI, 0.376–0.992; Fig. 2C).[9,14,15,17,26] When we performed subgroup analyses according to the study design, FIGO stage, and adjustment of confounding variables, HIPEC showed a favorable effect on DFS, whereas it failed to improve OS. However, HIPEC showed a favorable effect on OS for advanced, stage III-IV disease (HR, 0.748; 95% CI, 0.563–0.994; Table 2).[9,15,26]

For cases of recurrent disease, 5 studies including 357 patients did not show improved DFS after HIPEC (HR, 0.644; 95% CI, 0.395–1.049).[18,22–25] In particular, all these 5 studies targeted

Table 1

Characteristics of 15 studies about the effect of hyperthermic intraperitoneal chemotherapy on prognosis of ovarian cancer.

Study	Period of enrollment	Study design	Disease status	No. of patients		Criteria of optimal cytoreduction before HIPEC in subgroup analyses	Prognosis	Adjustment of potential confounding factors
				HIPEC	Non-HIPEC			
Ryu, 2004	1994–2000	Case-control	Primary	57	60	Residual tumor ≤1cm	DFS, OS	Age, stage, ECOG, size of residual tumor after the first surgery
Gori, 2005	1991–1997	Case-control	Primary	29	19	No visible tumor, residual tumor ≤1cm	OS	Age, stage, histology, grade
Muñoz –Casares, 2009	1997–2004	Case-control	Recurrent	14	12	Residual tumor ≤1cm	OS	Age, histology, grade
Kim, 2010	1991–2004	Case-control	Primary	19	24	No visible tumor, residual tumor ≤1cm	DFS, OS	Age, stage
Fagotti, 2012	2005–2009	Case-control	Recurrent	30	37	Residual tumor ≤1cm	DFS, OS	Age, stage, size of residual tumor after the first surgery
Warschkow, 2012	1991–2006	Case-control	Primary or recurrent	21	70	No visible tumor, residual tumor ≤1cm	OS	Age, stage, histology, grade
Cascales-Campos, 2014	1998–2011	Case-control	Primary	52	35	No visible tumor, residual tumor ≤1cm	DFS	Age, stage, grade, neoadjuvant chemotherapy, ECOG
Le Brun, 2014	1997–2011	Case-control	Recurrent	23	19	No visible tumor, residual tumor ≤1cm	OS	Age, stage, histology, size of residual tumor after the first surgery
Safra, 2014	Not mentioned	Case-control	Recurrent	27	84	No visible tumor, residual tumor ≤1cm	DFS, OS	Age, stage, size of residual tumor after the first surgery
Cascales-Campos, 2015	2001–2012	Case-control	Recurrent	32	22	No visible tumor, residual tumor ≤1cm	DFS	Age, stage, grade, ECOG
Spiliotis, 2015	2016–2013	RCT	Recurrent	60	60	Not performed	OS	Age, stage, size of residual tumor after the first surgery
Baiocchi, 2016	2000–2014	Case-control	Recurrent	29	50	Not performed	DFS, OS	Age, stage, histology
Marocco, 2016	1995–2012	Case-control	Recurrent	19	27	No visible tumor, residual tumor ≤1cm	DFS, OS	Age, stage, histology, grade
Mendivil, 2017	2012–2015	Case-control	Primary	69	69	No visible tumor, residual tumor ≤1cm	DFS, OS	Age, stage, histology, grade
Van Driel, 2018	2007–2016	RCT	Primary	122	123	Not performed	DFS	Age, stage, histology, neoadjuvant chemotherapy

DFS = disease-free survival; ECOG = Eastern cooperative oncology group performance status; HIPEC = hyperthermic intraperitoneal chemotherapy; OS = overall survival.

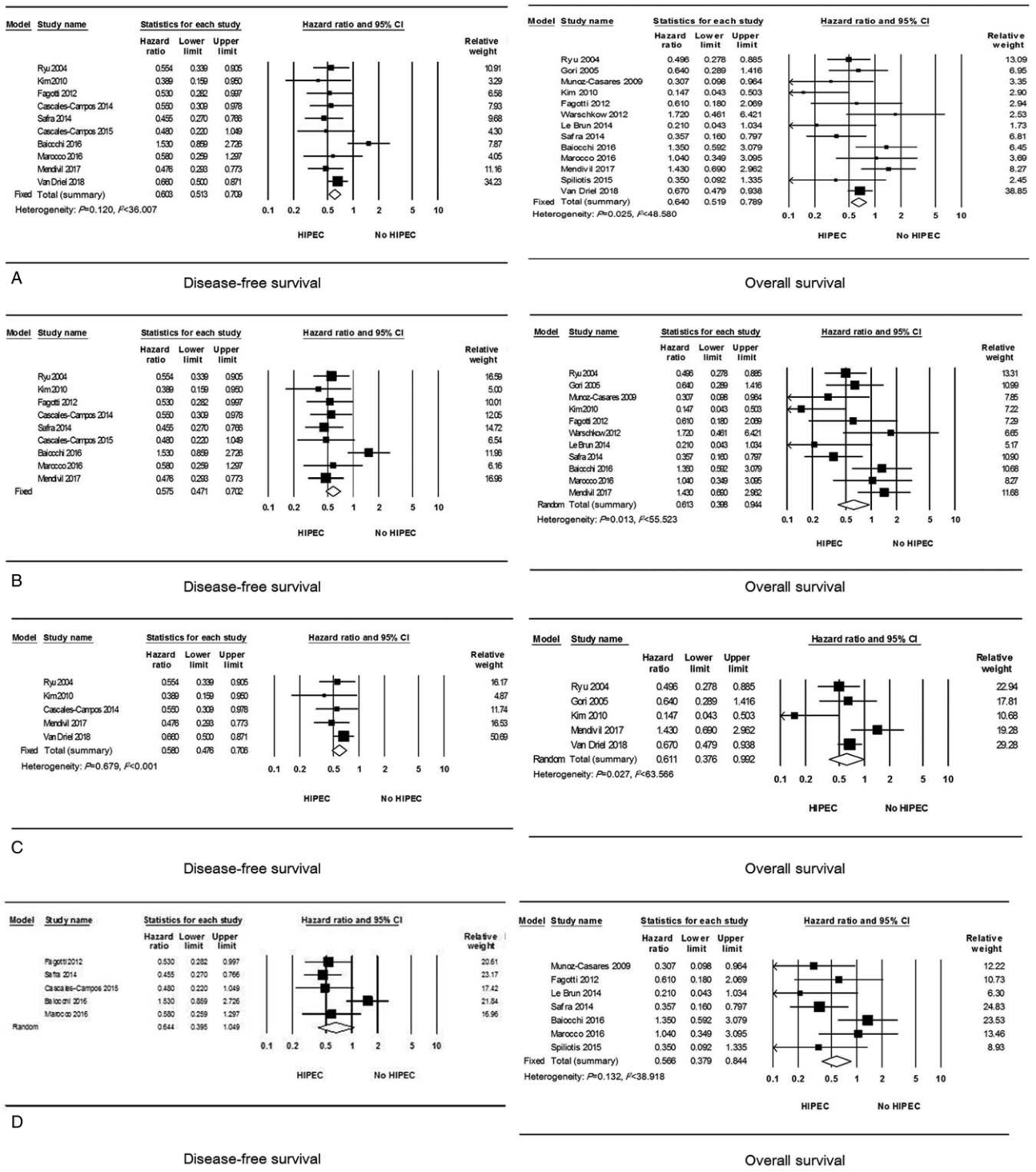

Figure 2. Effect of hyperthermic intraperitoneal chemotherapy (HIPEC) on survival by study design: (A) all studies; (B) case-control studies, and by disease status: (C) primary disease; (D) recurrent disease.

platinum-sensitive recurrent disease. On subgroup analyses according to the study design and quality of study, HIPEC failed to improve DFS. However, HIPEC showed better DFS after adjusting confounding variables (Table 3).

In terms of OS of patients with recurrent disease, 7 studies including 491 patients showed survival benefit after HIPEC (HR, 0.566; 95% CI, 0.379–0.844; Fig. 2D).[8,16,18,21,22,24,25] When meta-analysis was performed by including only 5 studies that targeted platinum-sensitive recurrent disease, HIPEC also showed a favorable effect on OS (HR, 0.616; 95% CI, 0.402–0.945).[18,21,22,24,25] On subgroup analyses according to the study design, quality of study, and adjustment of confounding

Table 2

Subgroup analyses for evaluating the effect of hyperthermic intraperitoneal chemotherapy on the survival of patients with primary disease.

	No. of studies	HR	95% CI	Heterogeneity		Model used
				P	I^2	
Disease-free survival						
Study design						
Case-control	4	0.508	0.383–0.672	.90	0.0%	Fixed effect
Stage						
III-IV disease	3	0.600	0.480–0.749	.49	0.0%	Fixed effect
Adjustment						
Age, stage, neoadjuvant chemotherapy	3	0.600	0.480–0.749	.49	0.0%	Fixed effect
Age, stage, histology, neoadjuvant chemotherapy	2	0.609	0.479–0.775	.25	24.0%	Fixed effect
Age, stage, grade, neoadjuvant chemotherapy, ECOG	2	0.505	0.349–0.732	.71	0.0%	Fixed effect
Overall survival						
Study design						
Case-control	4	0.563	0.265–1.196	.01	72.5%	Random effects
Stage						
III-IV disease	3	0.748	0.563–0.994	.17	44.5%	Fixed effect
Adjustment						
Age, stage, histology	3	0.748	0.563–0.994	.17	44.5%	Fixed effect
Age, stage, grade	2	0.972	0.443–2.137	.14	53.2%	Random effects
Age, stage, neoadjuvant chemotherapy	2	0.911	0.439–1.890	.06	70.9%	Random effects

ECOG = Eastern Cooperative Oncology Group performance status.

variables, HIPEC was consistently associated with better OS (Table 3).

3.3. Effect of HIPEC on survival by the extent of cytoreductive surgery

HIPEC significantly prolonged the DFS of patients with residual tumors ≤1 cm after cytoreductive surgery (HR, 0.488; 95% CI, 0.389–0.612)[14,17,18,20,22,23,25,26] and in those with no visible tumor (HR, 0.486; 95% CI, 0.377–0.628).[17,20,22,23,25,26] These results were also observed on subgroup analyses according to disease status, quality of the study, and adjustment of confounding variables (Table 4).

However, HIPEC did not increase OS of patients with no visible tumor (HR, 0.564; 95% CI, 0.310–1.027)[15,17,19,21,22,25,26] despite the improvement of OS of those

Table 3

Subgroup analyses for evaluating the effect of hyperthermic intraperitoneal chemotherapy on the survival of patients with recurrent disease.

	No. of studies	HR	95% CI	Heterogeneity		Model used
				P	I^2	
Disease-free survival						
Study design						
Case-control	5	0.644	0.395–1.049	.02	64.6%	Random effects
Quality of study (NOS)						
8	3	0.702	0.309–1.592	.01	81.1%	Random effects
Drug resistance						
Platinum-sensitive	5	0.644	0.395–1.049	.02	64.6%	Random effects
Adjustment						
Age, stage	4	0.489	0.359–0.690	.96	0.0%	Fixed effect
Age, stage, grade	2	0.526	0.300–0.922	.74	0.0%	Fixed effect
Age, stage, ECOG	2	0.510	0.312–0.833	.85	0.0%	Fixed effect
Age, stage, residual tumor size after surgery	2	0.484	0.324–0.723	.72	0.0%	Fixed effect
Overall survival						
Study design						
Case-control	6	0.593	0.390–0.902	.10	46.1%	Fixed effect
Quality of study (NOS)						
8	5	0.454	0.226–0.912	.08	52.1%	Random effects
Drug resistance						
Platinum-sensitive	5	0.616	0.402–0.945	.13	41.7%	Fixed effect
Adjustment						
Age, stage	5	0.616	0.402–0.945	.13	41.7%	Fixed effect
Age, stage, residual tumor size after surgery	4	0.437	0.253–0.756	.31	16.4%	Fixed effect

ECOG = Eastern Cooperative Oncology Group performance status; NOS = the Newcastle-Ottawa Scale.

Table 4

Effect of hyperthermic intraperitoneal chemotherapy on disease-free survival by the extent of cytoreductive surgery.

	No. of studies	HR	95% CI	Heterogeneity		Model used
				P	I^2	
Residual tumor ≤1 cm						
All studies	8	0.488	0.389–0.612	>.99	0.0%	Fixed effect
Primary disease	4	0.479	0.349–0.656	.93	0.0%	Fixed effect
Adjustment						
Age, stage, grade, neoadjuvant chemotherapy, ECOG	2	0.505	0.349–0.732	.71	0.0%	Fixed effect
Recurrent disease	4	0.498	0.359–0.690	.96	0.0%	Fixed effect
Quality of study (NOS)						
8	3	0.448	0.303–0.661	.94	0.0%	Fixed effect
Adjustment						
Age, stage, residual tumor size after surgery	2	0.484	0.324–0.723	.72	0.0%	Fixed effect
No visible tumor						
All studies	6	0.486	0.377–0.628	.99	0.0%	Fixed effect
Primary disease	3	0.486	0.345–0.685	.81	0.0%	Fixed effect
Adjustment						
Age, stage, grade, neoadjuvant chemotherapy, ECOG	2	0.505	0.349–0.732	.71	0.0%	Fixed effect
Recurrent disease	3	0.487	0.332–0.713	.88	0.0%	Fixed effect
Quality of study (NOS)						
8	2	0.463	0.300–0.713	.91	0.0%	Fixed effect
Adjustment						
Age, stage, grade	2	0.526	0.300–0.922	.74	0.0%	Fixed effect

ECOG = Eastern Cooperative Oncology Group performance status; NOS = the Newcastle-Ottawa Scale.

with residual tumors ≤1 cm after cytoreductive surgery (HR, 0.591; 95% CI, 0.431–0.811).[14–19,21,22,25,26] On subgroup analyses, HIPEC was effective for patients with recurrent disease who had residual tumors ≤1 cm after cytoreductive surgery (HR, 0.493; 95% CI, 0.315–0.773; Table 5).[16,18,19,21,22,25]

4. Discussion

The current meta-analysis provides further evidence that HIPEC may be associated with better survival of patients with ovarian cancer, and suggests how we can select patients with ovarian cancer who will benefit from HIPEC after cytoreductive surgery.

Considering the DFS, HIPEC was associated with better prognosis in patients with primary disease, whereas it failed to increase DFS of patients with recurrent disease. However, subgroup analyses revealed that HIPEC increased DFS of patients with residual tumors ≤1 cm and no visible tumor, regardless of primary or recurrent diseases. These results suggest that HIPEC may be effective for all patients with primary ovarian cancer, whereas its effect may be limited for those who underwent

Table 5

Effect of hyperthermic intraperitoneal chemotherapy on overall survival by the extent of cytoreductive surgery.

	No. of studies	HR	95% CI	Heterogeneity		Model used
				P	I^2	
Residual tumor ≤1 cm						
All studies	10	0.591	0.431–0.811	.06	47.4%	Fixed effect
Primary disease	4	0.590	0.255–1.362	.02	70.0%	Random effects
Adjustment						
Age, stage, grade, histology	2	0.443	0.443–2.137	.14	53.2%	Random effects
Recurrent disease	6	0.493	0.315–0.773	.39	4.8%	Fixed effect
Quality of study (NOS)						
8	4	0.394	0.230–0.676	.44	0.0%	Fixed effect
Adjustment						
Age, stage, residual tumor size after surgery	3	0.378	0.204–0.702	.57	0.0%	Fixed effect
No visible tumor						
All studies	7	0.564	0.310–1.027	.02	60.3%	Random effects
Primary disease	3	0.563	0.179–1.770	.01	79.8%	Random effects
Adjustment						
Age, stage, grade, histology	2	0.972	0.443–2.137	.14	53.2%	Random effects
Recurrent disease	4	0.525	0.308–0.894	.22	32.2%	Fixed effect
Quality of study (NOS)						
8	3	0.423	0.230–1.220	.30	18.0%	Fixed effect
Adjustment						
Age, stage, residual tumor size after surgery	2	0.522	0.110–2.465	.11	62.1%	Random effects

ECOG = Eastern Cooperative Oncology Group performance status; NOS = the Newcastle-Ottawa Scale.

optimal cytoreduction (residual tumors ≤1 cm and no visible tumor) for recurrent disease. The survival benefit from HIPEC in primary disease is in line with the RCT of van Driel et al in which HIPEC increased DFS of patients with ovarian cancer who received NAC followed by IDS.[9] After NAC, hidden tumors might still exist despite gross evaluation and optimal cytoreduction after IDS.[30] However, HIPEC may control both biologically residual and hidden tumors, resulting in a favorable prognosis.

For patients with recurrent ovarian cancer, improvement of DFS after HIPEC was observed only in those who achieved optimal cytoreductive surgery in this study. This limitation might have originated owing to the different biological properties of recurrent tumors because they commonly show drug resistance to chemotherapy.[31] Moreover, the penetration depth of chemotherapeutic drugs in HIPEC is limited to a few millimeters only.[32] Accordingly, the role of cytoreductive surgery may be particularly important for recurrent ovarian cancer, and optimal cytoreduction should be performed before the implementation of HIPEC because of drug resistance and limited penetration depth of the drugs used in HIPEC.

In terms of OS, HIPEC improved the prognosis in both primary and recurrent diseases. However, the effect of HIPEC was not observed in patients with primary disease who had residual tumors ≤1 cm or no visible tumors. In cases of primary disease, most of the tumors are naïve to systemic chemotherapy. In addition, we have to keep in mind that HIPEC has treatment-related complications as well.[33] Therefore, HIPEC might be unnecessary for patients with primary disease if optimal cytoreductive surgery is achieved and completion of planned cycles of adjuvant chemotherapy is expected.

The current meta-analysis showed that HIPEC did not increase OS of patients with recurrent ovarian cancer who had no visible tumor after cytoreductive surgery. However, the effect of HIPEC on OS could be expected in those who had residual tumors ≤1 cm after cytoreductive surgery. We do not know the exact reason, but one it is possible that HIPEC can increase the response of drug-resistant tumor cells to systemic chemotherapy. Previous studies have suggested that drug-resistant tumor cells with high amount of heat-shock proteins became more susceptible to the effect of hyperthermia,[34] and epigenetic alterations induced by hyperthermic chemo-perfusion altered the responsiveness to platinum agents.[35]

Nevertheless, this meta-analysis had some limitations. First, the different types of drugs used in HIPEC among the studies may result in bias. Second, the toxicity or adverse events of HIPEC were not evaluated. Third, most studies in this meta-analysis were retrospective studies except for the 2 RCTs.

Despite these limitations, the results of the current meta-analysis suggest the strong relationship between HIPEC and better survival of patients with primary or recurrent ovarian cancer. In particular, the results of this meta-analysis are significant, as they indicate which patients with ovarian cancer may benefit from cytoreductive surgery and HIPEC. However, additional relevant clinical trials are needed to select the appropriate patients and to demonstrate the effect of HIPEC on their prognosis in the near future.

Author contributions

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Funding acquisition: Hee Seung Kim.
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